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Environmental Criteria and
Assessment Office
Cincinnati OH 45268

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CRITERIA DERIVATION FOR THE POLYCYCLIC AROMATIC HYDROCARBONS

SUMMARY

The toxicity and carcinogenicity data for the polycyclic aromatic hydrocarbons (PAHs) have been reviewed in an effort to establish separate ambient water quality criteria (AWQC) for each of the 13 PAH compounds contained in the list of 129 priority pollutants. The following points were used to establish which chemicals should be included as priority pollutants:

1) They are frequently detected in ambient water.

2) Continuing production is expected either as a product or by-product.

3) Analytical attainability for identification and monitoring for standard purposes is achievable.

In providing specific information for each of these individual PAH chemicals, this document is intended to be more useful to the states for setting water quality standards than the previous PAH water quality document (U.S. EPA, 1980), which established one criterion for the entire class of PAHs.

The relevant literature for the last 2 years was reviewed. Data from acceptable studies, as well as information already presented in the existing AWQC document and the polycyclic organic matter (POM) document (U.S. EPA, 1979) were used in this evaluation.

There is sufficient information from which to conclude that BaP, DBA, BbF, IP, BaA and chrysene are carcinogens. There is sufficient information to conclude that BaP is carcinogenic by the oral route based on dietary administration to CFW mice and to derive a water quality criterion for BaP. These six compounds are carcinogenic to mice in skin painting experiments and are suspected to be carcinogenic by the oral route. With the exception of BaP, no acceptable oral carcinogenic tests have been done to confirm this suspicion. The seven other PAH compounds [acenaphthylene, anthracene,

benzo(k)fluoranthene (BkF), benzo(g,h,i)perylene (BP), fluorene, phenanthrene, pyrene] are classified as "incompletely characterized chemicals". They are defined as such since no evidence of carcinogenicity has been found either because skin painting tests were negative or because carcinogenicity testing was inconclusive, inadequate or not done and since, for some, even basic toxicity data are lacking.

Benzo(a)pyrene is the only PAH compound for which adequate data are available to set a water quality criterion. Only skin painting data are available for these other carcinogenic PAHs, and for the remaining compounds the available information is inadequate.

CRITERIA DERIVATION

For the maximum protection of human health for the potential carcinogenic effects due to exposure of BaP through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6} and 10^{-7}. The corresponding recommended criteria are 28.0, 2.8 and 0.28 ng/ℓ, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 311.0, 31.1 and 3.11 ng/ℓ, respectively.

An attempt was made to determine, from skin painting data, the potency of the other carcinogenic PAHs relative to BaP. The result was that the relative potencies of DBA, BbF, and the group consisting of BaA, IP and chrysene were roughly 1.0, 0.3 and 0.01, respectively, on a scale where the potency of BaP was 1.0. These relative potencies are only considered to be

rough estimates since they are based on an inappropriate route of administration. Consequently, the most that can be said in an attempt to give guidance for other PAH is that if the level of another PAH is less than the recommended criterion for BaP the resultant risk associated with this exposure will probably be less than the risk for BaP specified above. However, if the cumulative exposure to other PAH exceeds 28 ng/ℓ, the resultant risk could exceed 10^{-5}.

TABLE 1

Summary Information Relating to AWQC
for Selected Polycyclic Aromatic Hydrocarbons

Compound	Estimated AWQC at 10^{-5} (ng/ℓ)
CARCINOGENIC CHEMICALS	
Benzo(a)pyrene (BaP)	28
Dibenzo(a,h)anthracene (DBA)	S.D.
Benzo(b)fluoranthene (BbF)	S.D.
Indeno(1,2,3-c,d)pyrene (IP)	S.D.
Benzo(a)anthracene (BaA)	S.D.
Chrysene	S.D.
INCOMPLETELY CATEGORIZED CHEMICALS	
Acenaphthylene	I.D.
Anthracene	I.D.
Benzo(k)fluoranthene (BkF)	I.D.
Benzo(g,h,i)perylene (BP)	I.D.
Fluorene	I.D.
Phenanthrene	I.D.
Pyrene	I.D.

S.D. = Sufficient data to qualitatively assess health effects relative to BaP, but not to quantitatively estimate an AWQC.

I.D. = Insufficient data from which to calculate a criterion or qualitatively assess health effects.

BENZO(a)PYRENE

The ubiquitous presence of BaP in the environment has been documented in U.S. EPA (1980). Additional information has been provided through environmental monitoring; however, these data merely provide further documentation of the presence of this compound in the environment without indicating any change in the estimates of the extent of exposure. Human exposure to BaP occurs primarily through ingestion of food, followed by inhalation and the consumption of water. From the data presently available, it should be assumed that a large proportion, if not all, of the human population will be exposed to BaP in their daily activities.

There are only limited data on the toxicity of BaP following acute, subchronic and chronic exposures, with most of these data being obtained from observation during studies on BaP carcinogenesis. However, the lack of appropriate protocols and detailed observations makes these studies inappropriate for a toxicity-based criterion. No new information has been found to further define the toxic effects in either experimental animals or humans.

Benzo(a)pyrene has been well documented as an animal carcinogen when administered by skin painting, subcutaneous injection or inhalation. It is also a well-documented human carcinogen with evidence stemming back to 1775 when Percival Pott attributed the occurrence of scrotal cancer among chimney sweeps to their occupational exposure to soot (containing high concentrations of BaP). Since then, a number of such associations have been made.

Hammond et al. (1976) conducted a prospective study of mortality among 5939 male members of the United Slate, Tile and Composition Roofers, Damp and Waterproof Workers' Association between 1960-1971. The study was confined to members (active, probational, retired) with at least 9 years

employment. All death certificates were obtained through the union; follow-up was completed for 97.5% of the study population. Mortality among union members was compared with mortality among the total male U.S. population using a modified life-table approach. Occupational exposures as incurred by roofers were associated with excess mortality from lung cancer and cancers of other sites. Gradients of risk by length of exposure among roofers were demonstrated for lung, buccal, pharyngal, larynx, esophageal, stomach and bladder cancer. Exposure data were not collected for smokers or for PAHs other than BaP; how much of the excess mortality is due entirely to BaP cannot be determined from this study.

Earlier occupational studies noted an increase in lung cancer mortality among gas workers (Kennaway and Kennaway, 1936; Doll, 1952). Kennaway and Kennaway (1936) found an increased rate of bladder and lung cancer in occupations involving exposure to coal gas, tar, pitch and soot. In this study, the number of workers in any one occupational group was small, and it was not possible to calculate relative risks for exposed groups with certainty or to obtain evidence for a dose-response relationship.

In an effort to further quantify the Kennaway and Kennaway data suggesting a correlation between occupational exposure and cancer mortality, Doll (1952) studied the mortality among male pensioners (over age 60) of a large London gas works company for a 10-year period (1939 through 1948) and compared the data with mortality data for the population of Greater London. Men who retired early were included in the study on reaching 60, so as not to bias the investigation by the exclusion of a group who retired early because of health reasons. The pensioners' mortality from cancer was significantly in excess of the expected, with lung cancer accounting for the great-

est excess. When pensioners were categorized into low- and high-exposure groups, the excess lung cancer mortality among the high-exposure group was significant.

Coke plant workers exposed to BaP also demonstrated increased lung cancer (Reid and Buck, 1956; Lloyd, 1971). Reid and Buck (1956) conducted a mortality study in 1956 among 800 coke plant workers randomly selected from a total of 8000 employed over the years 1949-1954, inclusive. The study did not show an elevated cancer risk when death rates for all causes and for cancer were compared with age-specific rates prevailing in the period 1950-1954 among workers in a large unspecified industrial organization. The coke plant workers were categorized by occupation: coke oven workers, those handling by-products and maintenance workers (further grouped as laborers, workers and foremen). When occupational history was taken into account, no excessive cancer risk was found for by-product workers and only a small excess was found for men who had at some time worked at the oven.

This study was criticized by Lloyd (1971), who pointed out that Reid and Buck may have underestimated the number of lung cancer deaths, since the records included only men dying while still "on the books" during the period 1949-1954. Lloyd also states that "the population at risk and the distribution by age and area of prior employment were based on an estimate of figures which excluded retirees and those who had left employment." Lloyd undertook a 9-year prospective analysis of 2552 coke plant workers employed in 1953. He examined the mortality records of the workers in relation to length of employment and work area within the coke plant and compared the cause-specific mortality of coke plant workers as a whole with the mortality of the total steelworker population of 58,828 workers. Coke plant workers

were categorized as oven workers and non-oven workers. The excess lung cancer mortality among coke plant workers indicated that risk was elevated nearly 3-fold among coke oven workers.

These and other studies attributing increases in deaths due to lung, bladder, kidney and prostate cancers among persons occupationally exposed to BaP are reviewed in Environmental Quality Criteria for Polycyclic Organic Matter (U.S. EPA, 1979). Recent studies in animals have demonstrated the tumorigenic potential of BaP after *in utero* exposure and by intracolonic instillation. A number of new studies have further demonstrated that BaP is mutagenic in *in vitro* assays which have established strong correlations with the carcinogenic potential of a compound. Also, further studies on the metabolism of BaP provide supporting evidence that a metabolite of this compound is the ultimate carcinogenic species and that a large number of tissues are capable of metabolizing BaP.

Additionally, BaP has been tested in the mouse lung adenoma system by Shimkin and Stoner (1975). Following a single intravenous injection of ≈0.25 mg of aqueous dispersions of PAHs to strain A mice, a 100% response was obtained in the test animals. McCormick et al. (1981) exposed rats via gavage and observed a high number of mammary tumors among the exposed animals, given as number of tumors/animal (this study is discussed on page 14).

The only study available employing an appropriate route of exposure (oral) for criterion derivation is the study by Neal and Rigdon (1967). It is used to derive the ambient water quality criterion for BaP (U.S. EPA, 1980). Although this study has some clear deficiencies in experimental protocol, the carcinogenic response obtained was substantial. The deficiencies of this study included the use of animals of both sexes with no indication whether each group had the same proportion of each sex, the inclusion of

animals of various ages in each group, and the limited histological examination (only the digestive tract was examined for tumors). Although these deficiencies might preclude the use of this study to derive a criterion without supporting data, there are ample supporting data to indicate that BaP is tumorigenic in a variety of animals and tissues.

The most important deficiency of this study is whether the quantitative dose-response data are appropriate to use for a risk estimation because of the limited histological examination. These data may actually underestimate the risk of cancer, since tumors at other sites could have been present at lower doses than that which resulted in digestive system tumors; however, this is the only study which provides dose-response data following oral administration of BaP and until a better study is obtained on the carcinogenicity of benzo(a)pyrene, the study by Neal and Rigdon (1967) provides the best available quantitative information from which a criterion can be derived.

DIBENZO(a,h)ANTHRACENE

DBA is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion and has been found in ambient air, water, soils, sediment and food. From this, it is concluded that most, if not all, human populations are exposed to DBA. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that DBA would accumulate in the body with chronic low-level exposures.

The carcinogenicity of DBA to animals has been clearly established, and is supported by the results of numerous short-term genotoxicity assays and detailed metabolism studies. DBA has been tested in the mouse lung adenoma system by Shimkin and Stoner (1975), producing a 100% response in the test animals.

Information on the biological effects of DBA, when administered orally to animals, is very limited. Only one study has been identified which provides information on oral exposure (Snell and Stewart, 1962). DBA was administered to 14 male and 13 female mice at total dosages of 263 and 179 mg, respectively. However, this study has been determined to be unsuitable for criterion derivation due to necessary assumptions concerning the duration of exposure. Thus, while it is generally recognized that exposure to PAHs is associated with increased cancer risk in humans, the cancer data for DBA is considered to be inadequate for quantitative risk assessment and subsequent criterion derivation.

BENZO(a)ANTHRACENE

BaA is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and is commonly found in foods and ambient air. From this, it may be concluded that most, if not all, human populations are exposed to BaA. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that BaA would accumulate in the body with chronic low-level exposures.

There are no reports of BaA toxicity to humans. The only significant bioassay studies conducted with BaA are those which were designed to assess carcinogenic potential and do not provide sufficient information from which to derive a toxicity-based criterion. Therefore, due to insufficient data, a toxicity-based criterion for the protection of human health cannot be derived.

Similarly, the results of carcinogenicity bioassays, although creating concern for human health, do not provide the information necessary for extrapolation and criterion derivation. The deficiencies in these studies include: the route of administration (i.e., skin painting, subcutaneous

injection); exposure period (i.e., only a few doses administered); and scope of the study (i.e., too few animals; no histological examination). BaA has been tested in the mouse lung adenoma system by Shimkin and Stoner (1975), producing an 18% response in the test animals. The only oral ingestion study conducted with BaA was a 5-week study designed to determine the susceptibility of male mice to BaA-induced tumorigenesis (Klein, 1963). There are no published studies involving long-term feeding of BaA to animals. Thus, while it is generally recognized that exposure to PAHs is associated with increased cancer risk in humans, the cancer data for BaA is considered to be inadequate for quantitive risk assessment and subsequent criterion derivation.

INDENO(1,2,3-c,d)PYRENE

IP is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and has been monitored in foods, ambient air, water, soils and sediments. From this it may be concluded that most, if not all, human populations are exposed to IP. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that IP would accumulate in the body with chronic low-level exposures.

There are no reports of human health effects attributable to IP exposure. Similarly, there are no reported long-term animal bioassays which provide toxicity data other than information on tumor development by skin painting. Thus, there are insufficient data to presently derive a toxicity-based criterion for human exposure to IP.

Reports of tumor development in rodents administered IP by skin painting or subcutaneous injection create concern for potential consequences of human exposure. However, it is not presently possible to adequately assess the carcinogenic risk associated with IP based on the available animal data.

Thus, while it is generally recognized that human exposure to PAHs is associated with increased cancer risk, the cancer data for IP is considered to be inadequate for quantitative risk assessment and subsequent criterion derivation.

CHRYSENE

Chrysene is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, is commonly found in foods, and is monitored in ambient air. From this, it may be concluded that most, if not all, human populations are exposed to chrysene. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that chrysene would accumulate in the body with chronic low-level exposures.

There are no reports of chrysene toxicity to humans. The only significant toxicity studies conducted with chrysene are those which were designed to assess carcinogenic potential and do not provide sufficient information from which to derive a toxicity-based criterion. Therefore, due to insufficient data, a toxicity-based criterion for the protection of human health cannot be derived.

Similarly, the results of carcinogenicity bioassays on chrysene, although creating concern for human health, do not provide the information necessary for extrapolation and criterion derivation. Tumors produced by chrysene generally arise at the site of application following either subcutaneous injection or skin painting, or in the liver following intraperitoneal injection. There are no reported studies involving long-term feeding of chrysene to animals. While it is generally recognized that exposure to PAHs is associated with increased cancer risk in humans, the cancer data for chrysene is considered to be inadequate for quantitative risk assessment and subsequent criterion derivation.

BENZO(b)FLUORANTHENE

BbF is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and has been monitored in ambient air, foods, water, soils and sediments. From this it may be concluded that most, if not all, human populations are exposed to BbF. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that BbF would accumulate in the body with chronic low-level exposures.

There are no reports available concerning human exposure specifically to BbF. However, the carcinogenicity of BbF in animals has been well established. Tumors produced by BbF were observed at the site of application following either skin painting or subcutaneous injection. Bioassays of BbF involving oral exposure have not been reported, thus the available studies do not provide the information necessary for extrapolation and criterion derivation for human exposure. Nevertheless, the available data are sufficient to create concern over potential consequences of exposure to human health. While it is generally recognized that exposure to PAHs is associated with increased cancer risk in humans, the cancer data for BbF is considered to be inadequate for quantitave risk assessment and subsequent criterion derivation.

CRITERIA DERIVATION FOR THE CARCINOGENIC PAHs

BENZO(a)PYRENE

Neal and Rigdon (1967) exposed mice of both sexes via diet for 110 days. Seven exposure levels (including control) were used. Tumors were detected only in the forestomach. This study has been determined to be suitable for criterion derivation.

The second BaP study (McCormick et al., 1981) involved inbred virgin female LEW/Mai rats. The purpose of the study was to assess the inhibition of BaP-induced mammary carcinogenesis by retinyl acetate. However, a dietary control group of 20 animals received a single intragastric dose of 50 mg BaP, while another dietary control group of 20 animals received eight weekly fractions of 6.25 mg BaP. At 90 weeks, a tumor incidence of 77% was observed in the 50 mg group and a tumor incidence of 67% was observed in the 6.25 mg BaP group. All tumors were classified histologically as carcinomas but some were of a mixed type having elements of carcinoma and fibroadenoma. Also, several types of nonmammary tumors were found in these animals. One problem with this study is that the number of doses is small and the exposure duration is short: once per week for 8 weeks. Another difficulty concerns the study design. This assay was implemented to study inhibition of tumor induction, so that numbers of tumors per animal was the focus and not the number of tumor-bearing animals. The first issue is probably more serious since infrequent large doses are known to produce quite different blood levels than would smaller daily doses.

The water quality criterion for BaP is based on the experiment reported by Neal and Rigdon (1967), in which benzo(a)pyrene at doses ranging between 1 and 250 ppm in the diet was fed to strain CFW mice for ≈110 days. Stomach tumors, which were mostly squamous cell papillomas but also some

carcinomas, appeared with an incidence significantly higher than controls ($p<0.001$, Fisher Exact Test) at several doses. These data are fitted by a linearized multistage model and adjusted to approximate lifetime daily doses. The dose corresponding to a risk of 10^{-5} is determined by extrapolation. The data and parameters are as follows:

Dose (mg/kg/day)	Incidence† (No. responding/No. tested)
0.0	0/289
0.1	0/25
1.3	0/24
2.6	1/23
3.9	0/37
5.2	1/40
5.9	4/40
6.5	24/34
13.0	19/23
32.5	66/73

l_e = 110 days
L_e = 183 days
L = 630 days
w = 0.034 kg
R = 30 ℓ/kg

With these parameters, the carcinogenic potency factor for humans, q_1^*, is 11.53 $(mg/kg/day)^{-1}$. The result is that the water concentration of BaP should be <28 ng/ℓ in order to keep the individual lifetime risk below 10^{-5}.

DIBENZO(a,h)ANTHRACENE, BENZO(a)ANTHRACENE, INDENO(1,2,3-c,d)PYRENE, CHRYSENE, BENZO(b)FLUORANTHENE

In general, the data on these five compounds are limited. Although the data do suggest that these five compounds are carcinogenic, the available information is insufficient and comprises an incongruous set of data for use in criterion derivation. With such a lack of consistency between studies

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†The incidences at the highest three doses were not used in the extrapolation due to lack of fit of the multistage model. See the Human Health Methodology Appendices to the October 1980 Federal Register notice for a discussion on the fit of data to the multistage model (45 FR 79379).

and with additional limitations, the data base is not suitable for criteria derivation using the present, accepted methods as described in the Methodology and Guidelines (45 FR 79350-79355). However, the existing data base will be critically reviewed and alternate methods will be considered in an effort to use the available information and for the sake of thoroughness in assessing the human health risk associated with exposure to these compounds.

DBA and BaA are the only compounds considered here (other than BaP) that have been tested for carcinogenicity by oral administration to animals. However, both of these studies have characteristics which create uncertainty about the usefulness for assessing cancer potency from lifetime oral exposures.

The DBA study (Snell and Stewart, 1962) provides information for four potency estimates: alveolar carcinoma for both male and female mice, hemangioendothelioma for males and mammary carcinoma for females. The study involved chronic exposure via oral intake of an emulsion for roughly 200 days. The main drawback in the study is that exposure duration was only given as a range for each animal group. The midpoint of the range was used in subsequent calculations.

The purpose of the BaA study was to determine the susceptibility of male mice to tumorigenesis following oral exposure (Klein, 1963). Strain $B6AF_1/J$ hybrid infant mice were given 15 doses via stomach tube over a 5-week duration and observed for over 1 year. Both pulmonary adenomas and hepatomas were found at autopsy, but only hepatomas are used in the present calculations due to the high incidence of lung adenomas in the control group. The main source of uncertainty in using this study is the short duration of exposure. It is unlikely that effects from 15 doses would mimic effects from 600 doses, i.e., daily for a lifetime. When the actual daily

dose is computed, it is found to be ≈25-30 times higher than the estimated daily dose averaged over the length of the experiment. The end result is large, infrequent doses. Because this may be different from the lifetime situation involving daily exposure, extrapolation to lifetime is not recommended (i.e., effects due to high doses over a short time period may not be appropriate as models of effects due to low doses over lifetime).

Two oral studies were found for BaP. Potency estimates computed from these two studies are compared with the DBA and BaA potency estimates. These are given in Table 2. However, these estimates must be viewed with caution due to the issues discussed above. For the compounds where replicate potency estimates exist, it seems that the precision is within one order of magnitude. The potency estimates for DBA range from 0.57-2.4 $(mg/kg/day)^{-1}$, and those for BaP range from 0.28-0.71. The accuracy of these lifetime potency estimates is questionable because the extrapolation from short-term exposures to equivalent lifetime exposures is poorly understood. Any comparison between chemicals is further complicated by the differing exposure scenarios in the respective studies.

The effects from exposure via single intravenous injection upon strain A mice were studied by Shimkin and Stoner (1975) using BaP, DBA, BaA and other hydrocarbons. Both incidence data for the numbers of tumor-bearing animals and data on the numbers of tumors per animal were provided. Generally, the data are not presently useful for risk assessment purposes because the exposure was by a single injection and the observation period was only 13 weeks. Extrapolation from such an experiment to daily exposure for a lifetime, and the resulting lifetime incidence, is not well understood. More importantly, strain A pulmonary response is a specialized quick screening system, and biologically it is not equivalent to lifetime chronic bioassay of an animal

TABLE 2

Cancer Potency Estimates for Excess Risk of 10^{-5} from Lifetime Exposure
Based on Oral Exposure Data

Chemical	Species (sex)	Potency* $(mg/kg/day)^{-1}$	Tumor Type	Reference
BaA	mouse (M)	1.29	hepatoma	Klein, 1963
BaP	rat (F)	0.28 (0.61)	mammary carcinoma	McCormick et al., 1981
	mouse (M,F)	0.71	forestomach papilloma and carcinoma	Neal and Rigdon, 1967
DBA	mouse (M)	0.57	hemangioendothelioma	Snell and Stewart, 1962
	mouse (M)	0.75	alveolar carcinoma	Snell and Stewart, 1962
	mouse (F)	1.24	alveolar carcinoma	Snell and Stewart, 1962
	mouse (F)	2.36	mammary carcinoma	Snell and Stewart, 1962

*Potency estimate in parentheses is the mouse equivalent potency using mg per animal surface area as the equivalent dose.

species. In addition, for BaP and DBA the only incidences given for exposed groups are 100%, so that the dose used may not be the minimum which leads to 100% response. Thus, these data may underestimate the actual potency. The data on numbers of tumors per animal do not reach a limit as soon as incidence data and, thus, provide more precision for estimating potency. However, the methodology is not yet developed for using such data to estimate potency for subsequent risk assessment. Additionally, this test system has been criticized since strain A mice are highly susceptible to pulmonary adenomas and because of a high incidence of false negatives (Santodonato, 1982). Because of these difficulties, the Shimkin and Stoner (1975) study should not be used quantitatively but only qualitatively.

Finally, all five of these compounds and BaP have been tested for carcinogenicity through studies in mice given the test material by subcutaneous injection and through lifetime skin painting studies in mice. In addition to the unsuitability of the route of exposure for criterion derivation, the subcutaneous studies differ between compounds with respect to their study protocols, making direct comparison of carcinogenic potencies difficult. Conversely, for all six compounds, except BaA, a common protocol was employed in the skin painting studies by Wynder and Hoffman (1959); BaA was tested with a similar protocol, although with a different mouse strain, by Bingham and Falk (1969). Each skin painting study included BaP as a positive control agent justifying the comparison of each compound to BaP. Hence, these skin painting studies provide a common ground for at least a crude comparison of the carcinogenic potency of these six compounds. However, the results of these studies and any conclusions based upon them must be viewed with caution since these tests may reflect the tissue susceptibility of mouse skin to tumor formation. The findings may represent response

due to an unnatural exposure and, therefore, may not mimic the human response. With such uncertainties stated, and in the absence of carcinogenicity studies with oral administration of test material for each of these chemicals, this data set may be used for comparison of these compounds in terms of their carcinogenic potency.

These studies provide incidence data (i.e., mortality) for all five compounds and BaP, and time-to-tumor data for DBA, BbF, chrysene and BaP. Both the time-to-tumor and incidence data were evaluated in an attempt to estimate potencies for each of the six compounds. Although the time-to-tumor data were only available for four of the six compounds, they were incorporated into the statistical analysis for these compounds in an effort to use all available data. It is assumed that the combination of the time-to-tumor data with the incidence data will result in a better potency estimate.

Thus, estimates of potency (as either Q_1^* or q_1^* or ED_{10} or ed_{10}) based on these two kinds of data (time-to-tumor and incidence) are calculated for each compound adjusting for the length of the experiment, hence, making the studies directly comparable for a given estimate. The four indices are described below and are provided in Table 3.

For all six compounds, q_1^* and ed_{10} (and its 95% confidence limits) are calculated based on the incidence data alone. For BaP, DBA, BbF and chrysene, Q_1^* and ED_{10} (and its 95% confidence limits) are calculated based on the incidence data combined with the time-to-tumor data.

Q_1^* is the 95% confidence upper bound for the linear coefficient in the multistage model developed by Daffer et al. (1980) and evaluated at $t = 12$ months. The model uses time-to-tumor data for individual animals dying throughout the study. Twelve months was the longest survival time attained in all four compounds for which time-to-tumor data are available.

TABLE 3

Potency Indices for the Carcinogenic PAH Compounds Based on Skin Painting Data

Compound	Q_1^*	ED_{10} and 95% C.L.	q_1^*	ed_{10} and 95% C.L.	Reference
BaP	470	2.98×10^{-3} (8.62×10^{-4}, 5.98×10^{-3})	152.49	9.33×10^{-4} (6.54×10^{-4}, 1.21×10^{-3})	Wynder et al., 1957
BaP	435	1.43×10^{-3} (3.68×10^{-4}, 2.49×10^{-3})	67.62	1.71×10^{-3} (8.51×10^{-4}, 2.57×10^{-3})	Wynder and Hofmann, 1959
BaP	NA	NA	20.83	1.43×10^{-2} (4.24×10^{-3}, 2.44×10^{-2})	Bingham and Falk, 1969
DBA	299.62	6.34×10^{-4} (3.24×10^{-4}, 9.44×10^{-4})	292.81	6.16×10^{-4} (3.28×10^{-4}, 9.04×10^{-4})	Wynder and Hofmann, 1959
BbF	35.64	5.0×10^{-3} (2.75×10^{-3}, 7.25×10^{-3})	11.57	1.29×10^{-2} (8.54×10^{-3}, 1.73×10^{-2})	Wynder and Hofmann, 1959
Chrysene†	0.53	0.35 (0.23, 0.47)	0.88	0.21 (0.34, 1.12)	Wynder and Hofmann, 1959
BaA	NA	NA	0.28	0.73 (0.34, 1.12)	Bingham and Falk, 1969
IP	NA	NA	1.16	0.15 (0.08, 0.22)	Wynder and Hofmann, 1966

†Since there is only one dose group for chrysene, Q_1^* is calculated by using Kaplan-Meier survival analysis and the assumption that the control group has a zero response.

NA = Not available

Q_1^* = Estimate of carcinogenic potency based on the incidence data combined with the time-to-tumor data. It is the 95% confidence upper bound for the linear coefficient in the multistage model.

q_1^* = Estimate of carcinogenic potency based on the incidence data alone. It is the 95% confidence upper bound for the linear coefficient in the multistage model.

ED_{10} = Estimate of carcinogenic potency based on the incidence data combined with the time-to-tumor data as the effect dose associated with a risk of 10%.

ed_{10} = Estimate of carcinogenic potency based on the incidence data alone as the effective dose associated with a risk of 10%.

NOTE: For Q_1^* and q_1^*, higher numbers indicate increased potency whereas for ED_{10} and ed_{10}, lower numbers indicate increased potencies.

ED_{10} is the effective dose associated with a risk of 10%. The 10% risk is selected because it is the only response which is within the experimental dose range for all the compounds. Note that the ED_{10} (or ed_{10}) varies inversely with the potency estimate Q_1^* (or q_1^*) i.e., as Q_1^* increases, ED_{10} decreases.

The indices q_1^* and ed_{10} are the counterparts of Q_1^* and ED_{10}, but instead use only the incidence rates at the end of the study (≈20 months). The index currently used to reflect carcinogenic potency is q_1^*, which is the one-sided 95% upper confidence limit on the linear coefficient in the multistage model as revised by Crump (45 FR 79318). The indices Q_1^* (or q_1^*) and ED_{10} (or ed_{10}) are considered because it is desirable to compare compounds based on both an index (Q_1^* or q_1^*) which reflects the carcinogenic potency at low doses outside the experimental range, as well as an index (ED_{10} or ed_{10}) which reflects the carcinogenic potency within the experimental range. The latter approach presumably does not depend as much on the dose/response model used for the low dose extrapolation.

The potency estimates as given in Table 3 from each data type (i.e., Q_1^* vs. q_1^* or ED_{10} vs. ed_{10}) are not directly comparable. This is partly because consideration of early mortality (Q_1^*) leads to a higher potency estimate than would be obtained from incidence data alone (q_1^*). However, the time-to-tumor potency (Q_1^*) is based on a 12-month experiment duration, compared to ≈20 months for the incidence potency (q_1^*) which would decrease Q_1^* compared to q_1^*. The net effect of these positive and negative biases is not known.

Since there are three skin painting studies on BaP, the variability among each of the individual estimates can be examined. From the three incidence studies, a range of 21-152 or a 7-fold difference is noted among the estimates of q_1^*. This variability is also seen among the estimates of ed_{10} though not as apparent since the 95% confidence limits overlap between two of the three estimates. Estimates of Q_1^* and ED_{10} were calculated for BaP from two studies without the wide variability evident among the q_1^* and ed_{10} estimates.

Multiple studies are not available for the other five carcinogenic PAHs. Thus, the variability among the individual potency estimates cannot be examined. As outlined above, Q_1^* is not directly comparable to q_1^* and ED_{10} is not directly comparable to ed_{10}. However, potencies of each chemical relative to the potency of BaP are computed. Furthermore, the absolute accuracy of the four approaches for estimating potency is not well-understood as described above. The assumption is that the relative potency estimates are more accurate than the individual potency estimates. The estimates of relative potency of each chemical relative to the potency of BaP calculated via the four methods are provided in Table 4. The comparison is made to BaP since sufficient data justify the derivation of a water quality criterion for this chemical. Furthermore, it is one of the most potent and predominant PAHs, it is ubiquitous and well-characterized in the environment, and it is generally well understood making comparison to it most meaningful.

Since the BaP in Wynder and Hoffman (1959) is much more potent than the BaP in Bingham and Falk (1966), the carcinogenic potency of BaA which is also from Bingham and Falk (1966) is adjusted proportionally to make it comparable with the other compounds assuming any differences would be consistent between compounds.

TABLE 4

Potencies[a] of the Carcinogenic PAHs Relative to the Potency of Benzo(a)pyrene with the 95% Confidence Limits for the ED_{10} and ed_{10} Point Estimates

Compound	Relative Potencies[b]			
	$\frac{Q_1^* \text{ chemical}}{Q_1^* \text{ BaP}}$	$\frac{ED_{10} \text{ BaP}}{ED_{10} \text{ chemical}}$	$\frac{q_1^* \text{ chemical}}{q_1^* \text{ BaP}}$	$\frac{ed_{10} \text{ BaP}}{ed_{10} \text{ chemical}}$
BaP	1.0	1.0	1.0	1.0
DBA	0.69	2.3 (0.56, 5.3)	4.3	2.8 (1.3, 5.8)
BbF	8.2×10^{-2}	0.29 (0.071, 0.65)	0.17	0.13 (0.063, 0.24)
Chrysene	1.2×10^{-3}	4.1×10^{-3} $(1.1 \times 10^{-3}, 7.1 \times 10^{-3})$	1.3×10^{-2}	8.1×10^{-3} $(3.7 \times 10^{-3}, 1.7 \times 10^{-2})$
IP	-	-	1.7×10^{-2}	1.1×10^{-2} $(5.1 \times 10^{-3}, 2.6 \times 10^{-2})$
BaA	-	-	1.3×10^{-2}	2.0×10^{-2} $(5.5 \times 10^{-3}, 5.0 \times 10^{-2})$

[a] All potency estimates used in the ratios are given as animal potencies for lifetime exposure.

[b] The confidence limits for ED_{10} and ed_{10} were determined using Geary's theorem as given in Kendall and Stuart (1977, exercise 11.11). In all cases, higher numbers indicate increased potency.

Q_1^* = Estimate of carcinogenic potency based on the incidence data combined with the time-to-tumor data. It is the 95% confidence upper bound for the linear coefficient in the multistage model.

q_1^* = Estimate of carcinogenic potency based on the incidence data alone. It is the 95% confidence upper bound for the linear coefficient in the multistage model.

ED_{10} = Estimate of carcinogenic potency based on the incidence data combined with the time-to-tumor data as the effect dose associated with a risk of 10%.

ed_{10} = Estimate of carcinogenic potency based on the incidence data alone as the effective dose associated with a risk of 10%.

Based on the information pertaining to BaP in Table 3, it appears that ED_{10} (or ed_{10}) is a better index to use in establishing the relative potency among the six compounds. It is a better estimate based on its stability as compared to Q_1^* or q_1^*. As indicated in Table 4, the relative potencies based on ED_{10} and ed_{10} are quite consistent. There is no real difference between the estimates when compared for a given chemical (i.e., ED_{10} vs. ed_{10} for DBA, BbF and chrysene). In fact, the confidence limits also match quite well. It appears that the estimates can be combined using the ratios of ED_{10} when available, otherwise using ratios of ed_{10}. The comparison of relative potency using the linear coefficients (Q_1^* or q_1^*) shows less consistency. There are differences between the estimates of Q_1^* vs. q_1^* (i.e., for DBA and chrysene). In the worst case, chrysene, the difference is one order of magnitude. Since Q_1^* and q_1^* are upper confidence limits, they have no interval of variability around them to use for further judgment of comparability.

Ranking the compounds based on the relative potencies computed via the four methods, the following observations are made.

Q_1^*	q_1^*	ED_{10}	ed_{10}
BaP	DBA	DBA†	DBA†
DBA	BaP	BaP†	BaP†
BbF	BbF	BbF	BbF
Chrysene	IP†	Chrysene	BaA†
	Chrysene†		IP†
	BaA†		Chrysene†

†Not distinguishable

Based on the numerical properties alone, the relative potencies based on ED_{10} and ed_{10} seem most justifiable for use in ranking the chemicals since they are consistent. For example, for both estimates of relative potency, DBA is statistically similar to BaP since the confidence intervals for the relative potency include 1.0, the relative potency of BaP. BbF is statistically distinguishable as less potent than BaP, but more potent than chrysene. Due to confidence interval overlaps, chrysene, BaA and IP are not distinguishable.

Although the relative potencies of DBA and BaP are statistically similar based on both ED_{10} and ed_{10}, one cannot ignore the fact that for three of the four methods, DBA is consistently more potent than BaP. For this reason, and because of the poor oral data for DBA, we can only assume that DBA is at least as potent as BaP.

An uncertainty in the ranking is when the potency of BaA is adjusted to reflect the potency difference observed in the two different BaP studies (Wynder and Hoffmann, 1959; Bingham and Falk, 1969). It is assumed that the factors and their extent of influence which contribute to the discrepancy observed in the two BaP studies would also affect BaA in the same way with the same magnitude. This assumption may not be reasonable if, among other things, the mortality experience in the group exposed to BaP differed from the mortality experience in the group exposed to BaA. However, the uncertainty surrounding the similarities between BaA and BaP is minimized when the relative potency of BaA to BaP is calculated since they are both from the same study. This would indicate that the relative potency is a more accurate index than the individual potency estimate.

The question arises whether to calculate an index of relative potency based upon Q_1^* and q_1^* or ED_{10} and ed_{10}. We have already seen that the relative potencies based on ED_{10} or ed_{10} are more stable numerically and give more consistent ranking than the relative potencies which are based on Q_1^* or q_1^*. The advantage of using Q_1^* and q_1^* is that they are the potency estimates at low doses and are consistent with the previous criteria methodology. The water quality criterion for BaP is also estimated by q_1^* but this should not be considered relevant when one's interest is in estimating the best estimate of relative potency. The disadvantages of using Q_1^* and q_1^* are 3-fold. Since these estimates are computed from a confidence limit, a confidence interval is not provided. Furthermore, the magnitude of these estimates is dependent upon the sample size of the data used in the calculation. For example, given a constant rate of response the potency estimate increases as the sample size decreases due to the wider confidence interval. This wider interval gives a higher potency estimate since the upper confidence limit is used. As most of the studies on these compounds involve small samples, this dependence is strong. Finally, the low-dose extrapolation in the calculation of Q_1^* and q_1^* is model-dependent so that it must be assumed that the multistage model is appropriate for all compounds.

There are two advantages of using ED_{10} and ed_{10}. They are estimated within the experimental dose range. Therefore, they are less model-dependent and possess some statistically optimal properties. Secondly, the computation of these indices provides a confidence interval. The disadvantage of using these indices is that one must assume that the relative potency estimate would also hold in the low-dose range. The shape of the dose-response curve is highly chemical-specific, so this last assumption may not be valid.

Thus, it becomes apparent that although ED_{10} (or ed_{10}) appears to be the best index, neither index to estimate relative potency is clearly the best. Yet, it is conceivable that these relative potencies might be used to compute individual water quality criteria for these compounds. Several deficiencies involved in using either Q_1^* (or q_1^*) or ED_{10} (or ed_{10}) are outlined above. However, regardless of the approach taken, serious uncertainties remain:

1. It is unknown if the relative cancer potency as calculated from skin painting studies approximates and is applicable to the relative cancer potency from chronic oral exposure.

2. It is unknown if the mortality experiences of the study population for a compound is similar to that of the study population for BaP.

3. It has not been demonstrated that the relative potency is more accurate than the individual potencies.

4. Due to the lack of consistency in the data both between and among the compounds, the accuracy of the data cannot be assured.

Although limitations in the available oral data have been identified, these data can be used to test the assumption that potency (or relative potency) is independent of exposure or route. Due to uncertainties and inconsistencies in the data, it is more appropriate to test this assumption using the relative potency to BaP rather than the actual potency estimates themselves. The potency ratios of DBA and BaA to BaP based on the oral and skin painting data are provided in Table 5. The data provided in Table 2 are used to compute the oral relative potencies.

The variability in the potency ratios among the DBA oral estimates is most obvious. More important are the relation of DBA and BaA to BaP based on the two sets of data. In the oral studies, DBA and BaA are both more

potent than BaP (the average of the DBA ratios is 1.8). In the dermal situation, both DBA and BaA are less potent than BaP. Thus, these data do not validate the assumption of BaP being the most potent of these six PAHs. However, due to the problems associated with these data, as previously outlined, it cannot be concluded that the assumption is false, but only that it is unverified by the skin painting studies.

The number of tumors per animal as provided in the mouse intravenous studies might also conceivably be used to test this assumption of BaP being most potent once a methodology to use such information to estimate carcinogenic potency is developed, accepted and verified. Following acceptance of this methodology, the data from this study and additional studies can be evaluated. The carcinogenic potencies can be further used to test the assumption of equivalence in potency among compounds between routes of exposure. The additional studies are the single dose oral studies by McCormick et al. (1980, 1981) and the skin painting studies by Burns and Albert (1982). The U.S. EPA's Carcinogen Assessment Group has access to the raw data from these studies and is presently examining these issues.

Considering these assumptions and uncertainties, it is recommended that the relative potencies be compared in a qualitative evaluation of these compounds. Only qualitative statements are appropriate in predicting the risk associated with oral exposure to these compounds from the skin painting data. But perhaps more importantly, it must be recognized that the occurrence of any one of the PAH compounds in the environment signals a very complex exposure situation. The individual compounds would rarely occur alone but do occur in complex mixtures of which little is known. Future research providing quantitative information should concentrate on the individual compounds as well as their interactions.

TABLE 5

Potencies of DBA and BaA Relative to the Potency of BaP* Using Oral and Skin Painting Data

Compound	Oral	Skin
BaP	1.0	1.0
DBA	0.8 1.1 1.8 3.3	0.7
BaA	1.8	0.1

*From Table 2, the oral potency of BaP for this calculation is taken to be 0.71 $(mg/kg/day)^{-1}$.

The uncertainties in the available data cannot be overlooked as they indicate how little we know about these compounds in terms of the health risks associated with exposure to them. Thus, the lack of consistent health data along with the exposure uncertainties indicate that the quantitative evaluation of these compounds would be premature. Not only do we lack data suitable for criterion derivation and data providing consistent potency estimates, but also the more basic data and information on the occurrence and behavior of these compounds in the environment as complex mixtures. Until such data are available, any quantitative evaluation of these compounds will be questioned and could be meaningless, thereby rendering it ineffective. It should be recognized that the data are sufficient to conclude that these compounds are carcinogenic but are insufficient to quantitatively evaluate the cancer risk. Thus, pending additional information, only the qualitative evaluation of these five compounds is justified. This may be done by reviewing the data bases for these five compounds as provided in Environmental Quality Criteria for Polycylic Organic Matter (U.S. EPA, 1979) and Ambient Water Quality Criteria for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1980), and by using the skin painting studies to qualitatively evaluate each compound relative to the carcinogenic potency of BaP.

In summary, oral, subcutaneous and mouse lung data are available for different subgroups of the six carcinogenic PAHs. Mouse skin painting data are available for all of the compounds. Due to the inadequacy of the oral, subcutaneous and lung data for criteria derivation and because skin painting data are available for all of the compounds, the skin painting data are used in estimating the carcinogenic potency of these compounds relative to BaP.

Following the thorough evaluation of all possibilities, it is concluded that the skin painting data can be used to estimate a potency for each compound relative to the potency of BaP. This is done since: 1) BaP is one of the most potent PAHs; 2) of the PAH compounds of interest, BaP is the most widely studied in terms of its carcinogenicity; 3) of the PAH compounds of interest BaP is one of the most predominantly found PAHs in the environment; and 4) due to the adequacy of the oral data, BaP is the only compound of interest for which an ambient water quality criterion is available. It appears preferable to calculate relative potency by using the potency estimate of ed_{10}, unless a better estimate for ED_{10} is available. Regardless of the individual potency estimate used, the use of relative potencies to calculate individual water quality criteria is fraught with uncertainties. For this reason, among others, only a qualitative evaluation of these five carcinogenic PAHs is recommended. Scientific investigation of all data indicate that relative to BaP the ranking of these chemicals based on carcinogenic potency is BaP $\geq$ DBA > BbF > BaA $\geq$ IP $\geq$ chrysene. If necessary, the most that can be said in an attempt to give guidance for these carcinogenic PAHs is that if the level of another PAH is less than the recommended criterion for BaP, the resultant risk associated with this exposure will probably be $<10^{-5}$. However, if the cumulative exposure to other PAHs exceeds the criterion recommended for BaP, the resultant risk may exceed 10^{-5}.

INCOMPLETELY CATEGORIZED CHEMICALS

ACENAPHTHYLENE

There is no information available concerning the presence of acenaphthylene in the environment or the extent of human exposure to acenaphthylene. Similarly, there are virtually no data available regarding the biological activity of acenaphthylene in humans or animals. Thus, it is not possible to recommend a toxicity-based criterion for human exposure to acenaphthylene.

ANTHRACENE

Anthracene is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and has been detected in foods and ambient air. From this it may be concluded that most, if not all, human populations are exposed to anthracene. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that anthracene would accumulate in the body with chronic low-level exposures.

Little is known regarding the human or animal toxicity of anthracene. It is reportedly non-carcinogenic and non-mutagenic in several test systems. There are no studies available from which a criterion can be derived for the protection of human health. Thus, it is not possible to recommend a toxicity-based criterion for human exposure to anthracene.

BENZO(k)FLUORANTHENE

BkF is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and has been monitored in ambient air and water. From this it may be concluded that most, if not all, human populations are exposed to BkF. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that BkF would accumulate in the body with chronic low-level exposures.

Data on the toxicity of BkF are very limited. There are no reports of health effects resulting from human exposure specifically to BkF. Animal studies are limited to skin painting experiments with mice. Thus, it is not presently possible to derive a toxicity-based criterion for human exposure to BkF.

Reports of the marginal carcinogenic and mutagenic acitivity of BkF create concern over possible consequences of human exposure. However, such information provides insufficient evidence from which to draw a conclusion of carcinogenicity. A suitable study is not available from which an ambient water quality criterion can be derived for the protection of human health. Thus, it is not possible to recommend a toxicity-based criterion for human exposure to BkF.

BENZO(g,h,i)PERYLENE

BP is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and has been detected in foods and ambient air. From this it may be concluded that most, if not all, human populations are exposed to BP. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that BP would accumulate in the body with chronic low-level exposures.

Very little has been reported regarding the biological activity of BP. There are no reports of health effects resulting from human exposure specifically to BP. It is reportedly non-carcinogenic, but has displayed both positive and negative results in the Ames Salmonella mutagenicity assay. Thus, there are no suitable studies available from which an exposure criterion can be derived for the protection of human health. Therefore, it is not presently possible to recommend the derivation of a toxicity-based criterion for human exposure to BP.

FLUORENE

There is very limited information on the extent of human exposure to fluorene; however, fluorene has been detected in drinking water, smoked food and fly ash. Although an estimate cannot be made presently on the extent of exposure to fluorene, the formation of this compound as a by-product of combustion may mean that extensive exposure occurs. The only health effects data available on fluorene are two mutagenicity studies and a tumor initiation study. All of these studies indicate that fluorene has no biological activity; however, mutagenicity and tumor initiation studies by themselves are insufficient to support a toxicity- or carcinogenicity-based human risk criterion. Until further information becomes available on the exposure and health effects of fluorene, there is insufficient data to derive a criterion.

PHENANTHRENE

Phenanthrene is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and has been repeatedly detected in foods and ambient air. From this it may be concluded that most, if not all, human populations are exposed to phenanthrene. Based on the ability of mammals to rapidly metabolize PAH, it is not expected that phenanthrene would accumulate in the body with chronic low-level exposures.

There are no reports of health effects resulting from human exposure to phenanthrene; similarly, little is known regarding the toxicity of phenanthrene to animals. It is reportedly non-mutagenic and non-carcinogenic, although positive results have been obtained by a few investigators using genotoxicity screening systems. A suitable study is not available from which an exposure criterion can be derived for the protection of human health. Thus, it is not possible to recommend a toxicity-based criterion for human exposure to phenanthrene.

PYRENE

Pyrene is assumed to be ubiquitous in the environment; it is a natural product of incomplete combustion, and has been monitored in food and ambient air. From this, it may reasonably be concluded that most, if not all, human populations are exposed to pyrene. Based on the studies of Mitchell and Tu (1979) and our knowledge of the rapid metabolism of PAHs in general, it is not expected that pyrene would accumulate in the body with chronic low-level exposures.

There are no available reports concerning the toxicity of pyrene to humans. The available information concerning the biological activity of pyrene in animals is too limited to allow for derivation of a toxicity-based criterion for human exposure. The present data appear adequate only to support the conclusion that pyrene is not carcinogenic.

CRITERIA DERIVATION FOR THE INCOMPLETELY CHARACTERIZED PAHs

ACENAPHTHYLENE, ANTHRACENE, BENZO(k)FLUORANTHENE, BENZO(g,h,i)PERYLENE, FLUORENE, PHENANTHRENE, PYRENE

The decision to classify these compounds as incompletely characterized is based on the diverse data bases for each. There are skin painting studies for BP, fluorene and pyrene, skin painting studies and a subcutaneous study for anthracene, and a study involving exposure via intraperitoneal injection for phenanthrene. There are no data available on acenaphthylene.

For all six of these compounds, there are insufficient data upon which to recommend a toxicity-based criterion for human exposure.

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